

Patient-specific induced pluripotent stem cells as a model for familial dilated cardiomyopathy.

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Public Summary:

Heart failure due to genetic mutation is one of the most common ailment and is a major contributor to the large number of patients on the heart transplant. One form of this heart failure is call dilated cardiomyopathy. Earlier studies have found that this disease is caused by mutation in a cardiac muscle gene call troponin T. In this study a special stem cell was generated from the skin cell of a family of patients with this mutation as well as their non-diseased sibling. The results from this study shows that the heart muscle cells derived from the special stem cell from these patients have abnormal regulation of their calcium level and led to decreased ability to contract as a muscle cell. These cells also show abnormal display of muscle protein structure. When these diseased cells are treated with a drug that accelerates the beating, they show compromised contraction and even more abnormal display of muscle protein structure. Expectedly, treatment of these cells with drugs that protect against rapid beating led to improvement of muscle cell contraction. Hence these stem cell-derived heart muscle cells provide a way to directly study the responses of these cells to specific drugs and may be useful for personalized therapy or as a model to screen for new drugs against heart failure.

Scientific Abstract:

Characterized by ventricular dilatation, systolic dysfunction, and progressive heart failure, dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in patients. DCM is the most common diagnosis leading to heart transplantation and places a significant burden on healthcare worldwide. The advent of induced pluripotent stem cells (iPSCs) offers an exceptional opportunity for creating disease-specific cellular models, investigating underlying mechanisms, and optimizing therapy. Here, we generated cardiomyocytes from iPSCs derived from patients in a DCM family carrying a point mutation (R173W) in the gene encoding sarcomeric protein cardiac troponin T. Compared to control healthy individuals in the same family cohort, cardiomyocytes derived from iPSCs from DCM patients exhibited altered regulation of calcium ion (Ca²⁺), decreased contractility, and abnormal distribution of sarcomeric alpha-actinin. When stimulated with a beta-adrenergic agonist, DCM iPSC-derived cardiomyocytes showed characteristics of cellular stress such as reduced beating rates, compromised contraction, and a greater number of cells with abnormal sarcomeric alpha-actinin distribution. Treatment with beta-adrenergic blockers or overexpression of sarcoplasmic reticulum Ca²⁺ adenosine triphosphatase (Serca2a) improved the function of iPSC-derived cardiomyocytes from DCM patients. Thus, iPSC-derived cardiomyocytes from DCM patients recapitulate to some extent the morphological and functional phenotypes of DCM and may serve as a useful platform for exploring disease mechanisms and for drug screening.

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